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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
05/05/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/528,343	ISOBE ET AL.	
	Examiner	Art Unit	
	/Mark L. Berch/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/20/2009* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89-108 and 110-132* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *122 and 124-131* is/are allowed.

6)☒ Claim(s) *89-108,110-121 and 123* is/are rejected.

7)☒ Claim(s) *132* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/20/2009 has been entered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 89-99, 109, 111-113, 121 are rejected under 35 U.S.C. 102(b) as being anticipated by 6329381.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 89-99, 110-113, 121, are under 35 U.S.C. 103(a) as being unpatentable over 6329381.

See Formula I in general, and examples 39-40, with Q1 as COOMethyl and example 45, with Q1 as $CONH_2$, with the 9-position having unsubstituted benzyl in each case, X1=S, Y1 as methylene or ethylene or propylene. Immune modulation is taught at column 127, line 39-40; treatment of allergies in claim 13. Although asthma of claim 110 is not specifically mentioned it would be obvious, as it is one of the most common allergic conditions, especially in children.

In fact, the reference compounds even operate by the same mode of action, i.e. inducing interferon activity, now recited in claim 121. See e.g. claim 13 of the reference, and Table 1, which measures exactly this activity. In the instant specification, see page 39, lines 4-5, page 40, line 8, and Table 2, which measures exactly this activity.

A transdermal formulation is disclosed at column 20, line 40. A transdermal formulation meets the claim language, as it is applied directly to the skin. Further, line 40 mentions propellants, which are used only in sprays, which again are used topically. Accordingly, all elements of the claims are disclosed, and the claims are anticipated.

Although there are no actual working examples of a transdermal composition or a spray, that is not required: "anticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabled to one of skill in the art." (***Bristol-Myers Squibb Co. v. Ben Venue Labs. Inc.***, 58 USPQ2d 1508).

Alternatively, it would be obvious to prepare such compositions, as that is exactly what the specification teaches, even if no specific formulations are set forth.

In short, the reference teaches applicants compound, for applicants utility, with applicants' mode of action, and teaches transdermal compositions, which are applied to the skin, and teaches propellants, which are used only for sprays, i.e. compositions that are applied to the skin, or used for inhalants.

The earlier traverse was unpersuasive. Applicants stated: "With respect to the method claims 89-99 and 115-119, these claims relate to administration for regulating an immune response (e.g. line 2 of claim 89)." Agreed, and true of claim 114 as well. Applicants continued:

"Nowhere in the reference is there any teaching or suggestion of topical administration of any compound as in the present claims. Such route of administration disclosure as is presented by '381 is at col. 20, lines 34-42, and only oral or parenteral administration, i.e. systemic routes of administration are disclosed."

This is simply untrue. Applicants have ignored the portions of the reference which the examiner has pointed to. The reference teaches transdermal. A transdermal medicine is by its very nature topically applied. Dermis means skin. Transdermal formulations e.g. typically ointments or patches, are applied to the skin. Thus, applicants "only oral or parenteral" is simply not true.

In addition, the line 40 mentions propellants, which are used only in sprays. Sprays actually have two uses, into the lungs, and, again, onto the skin. To rebut applicants' arguments, there is cited purely as an example, 5792793, which teaches at column 4, line 34 the compounds as "antibacterial, antifungal, and antiviral sprays." The following paragraph discusses the use of propellants, although of course one of ordinary skill in the art would already know that propellants are used to make sprays. The use of these

compounds on skin is referred to in many places e.g. last sentence of abstract, sentence bridging columns 1-2. This is then presented as evidence that one of ordinary skill in the art would understand that the use of propellants conveys that the compounds can be used to spray a compound onto skin, a topical route.

The claim as presently amended ends with "and wherein said medicament shows an effect only at the applied location". For reasons set forth below, this is indefinite, and cannot be relied on to distinguish over the art.

Applicants' remarks of 02/23/2009 are not useful in places, and not understood in other places. The remarks state, "Applicants first point out that claims 89 and 90 have been amended. Applicants submit that those amendments remove the present claims from the scope of the prior art." No specific explanation for this is provided. The claim now says allergies, but the examiner has pointed out that claim 13 in the reference has allergic diseases.

In other places, the examiner is at a loss to understand applicants' reasoning. For example, from the first page of the rebuttal arguments (page 21): "The Examiner states that it is "simply untrue" that transdermal administration is not equivalent to topical administration." That is not what the examiner stated. From page 4:

response (e.g. line 2 of claim 89)." Agreed, and true of claim 114 as well. Applicants continue:

"Nowhere in the reference is there any teaching or suggestion of topical administration of any compound as in the present claims. Such route of administration disclosure as is presented by '381 is at col. 20, lines 34-42, and only oral or parenteral administration, i.e. systemic routes of administration are disclosed."

This is simply untrue. Applicants have ignored the portions of the reference which

What the examiner was saying was untrue was applicants' description of the reference. The examiner was not saying anything about what is equivalent to what.

The remarks continue: "The Examiner concludes that "[a] transdermal medicine is by its very nature topically applied. Dermis means skin. Transdermal formulations . . . are applied to the skin." (Office Action, page 4). Applicants submit that a topical administration is NOT a systemic administration."

This is a total non-sequitur. The portion of the examiner's statement which was quoted had nothing at all to do with the relationship between topical administration and systemic administration. Furthermore, it's irrelevant. The term "systemic administration", or its equivalent did not appear in the rejected claims, and the claim was silent as to whether the administration was systemic or was not systemic.

Next, applicants stated, "Moreover, the Examiner should only take official notice of a fact, unsupported by documentary evidence only when it is "common knowledge in the art" which is "capable of instant and unquestionable demonstration as being well known." (MPEP 2144.03(A))."

What exactly is the point here? Yes the examiner states that "transdermal medicine is by its very nature topically applied" is "common knowledge in the art". The statement "Dermis means skin" and the statement "Transdermal formulations . . . are applied to the skin" are likewise "common knowledge in the art".

To give another example, the next page has

"Sprays

The Examiner states that '381 mentions "propellants which are used only in sprays... [which] have two uses, into the lungs, and again, onto the skin." However, in the claim

directed to "inhalation" the ring A is recited as being a heteroaromatic ring (claims 100-106), or in instances where ring A is benzene, the ring A is substituted by an alkyl amino substituted ester group (claims 107-114). The particular compounds of claim 120 are not mentioned in the '381 patent either. Thus, Applicants request that the Examiner withdraw the rejection regarding claims 113 and 120."

The examiner did indeed argue that the reference teaches sprays, and that sprays, whether administered to the skin or to the lung, is a form of topical administration. But what is this "the claim directed to "inhalation"..."? Claims 100-106 are not method claims, and are not in fact rejected over the reference. As for "withdraw the rejection regarding claims 113 and 120", claim 120 is not rejected over the reference. As for claim 113, that is rejected, but the claim is dependent on claim 90, not claim 100. Claim 90, unlike claim 100, is not required to have A as a heteroaromatic ring, nor is it the case that "the ring A is substituted by an alkyl amino substituted ester group" in claim 113. That is, while applicants lump together claims 107-114 as where ring A is benzene, the ring A is substituted by an alkyl amino substituted ester group, this is simply not true for claim 113.

Applicants are simply confused about the claims.

Claims 111-112 recite a physiological property. This exact property does not appear in the reference. MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the e.g. half life. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is the half-life.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. In every reference applied, the reference explicitly teaches exactly what the compound is. In fact, it is the opposite. In a normal inherency situation, the claim is of known structure, and the reference is of unknown structure. Here, the reverse is true, and hence the legal circumstances of inherency-in-the-prior-art do not apply. The only difference is the property about which the reference happens to be silent. Recitation of a property, inherently possessed by the prior art thing, does not distinguish a claim drawn to those things from the prior art, ***In re Swinehart***, 169 USPQ 226, 229.

See for example ***Ex parte Anderson***, 21 USPQ 2d 1241 at 1251, discussion of Rejection E. The claims had "numerical or functional values for certain properties which [the authors of the references] did not measure". The PTO presented no reasoning as to why the prior art material would have been expected to have those properties. Instead, the decision states, "There is ample precedent for shifting the burden to an applicant to

reproduce a prior art product whose final structure or properties are, at least, in part determined by the precise process used in its manufacture." (page 1253).

In another example, certain claims of ***Ex parte Raychem Corp.*** 25 USPQ2d 1265 required a linearity ratio of less than 1.2. The decision notes that neither reference discloses any values of the linearity ratio. The PTO presented no reasoning as to what the ratio would be expected to be in the references. The Decision states: "However, this does not end the inquiry since, where the Patent and Trademark Office is not equipped to perform the needed testing, it is reasonable to shift the burden of proof to Raychem to establish that (1) the argued difference exists...."

And indeed, there have been a number of cases in which applicants have pointed to silence of the prior art with regard to this or that property: ***In re Pearson***, 181 USPQ 641; ***In re Zierden*** 162 USPQ 102; ***In re Lemin***, 140 USPQ 273; ***Titanium Metals Corporation of America v. Banner***, 227 USPQ 773; ***In re Benner,*** 82 USPQ 49; In re Wilder, 166 USPQ 545; ***Ex parte Kucera***, 165 USPQ 332; ***General Electric Co. v. Jewel Incandescent Lamp Co.***, 67 USPQ 155; ***In re May***, 574 F.2d 1082, 1090, 197 USPQ 601, 607; ***In re Parker***, 43 USPQ 457. Such efforts to avoid anticipation on that basis invariably failed. Going further, if silence about properties of prior art compounds could be relied on, then one could not reject over references with no utility (see ***In re Schoenwald***, 22 USPQ2d 1671), since applicants could always insert the utility into the claim as a property.

It is well settled that the PTO can require an applicant to establish that a prior art product does not necessarily possess the characteristics of the claimed product when the prior art and claimed products are identical or substantially identical. An applicant's

burden under these circumstances was described in ***In re Best***, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977) as follows:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. . . . Whether the rejection is based on 'inherency' under 35 U.S.C. § 102, or 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products (footnote omitted).

The earlier traverse was unpersuasive. Applicants refer to this as "an inappropriate stretching of the law of inherency." As explained above, however, this is not a normal inherency situation, as it is known what the compounds are. It is simply a matter of the reference being silent on the silence of the reference on the half-life of the compound in liver S9. The MPEP quote above clearly covers this exact situation. Similarly, applicants state, "An argument that a "similar" compound will have identical properties is inappropriate." The examiner does not make that argument. The genus of these claims embraces compounds of the prior art. The examiner does not rely on similarity of compounds.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 89-99, 110-113, 115-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The new language "and wherein said medicament shows an effect only at the applied location" lacks description in the specification. This property, either in these words or in some other equivalent language, simply does not exist in the specification.

Claim 121 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Where exactly in the specification is this exact property of not raising recited? The remarks state, "New claims 121-131 have been added. Support for these claims is found in the originally filed claims." This is totally mistaken. Original claims 1-46 made no mention of interferon, and indeed, there weren't any method claims at all.

Claims 89-99, 110-113, 115-119 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new language "and wherein said medicament shows an effect only at the applied location" is indefinite.

First, what does it limit? Does it limit the compound, i.e. does it exclude those compounds which fail to meet this claim limitation? Or does it limit the method of treating, i.e. one does the treating in such a way that the claim limitation can be met. And if the latter is true, how is that done? This is a result, but there is no step to say how this is done.

Second, it is by no means clear how one can determine that the limitation has been met, because it involves proving a negative. If there were so much as one single effect outside the location, then the claim limitation is not met. How could one show that this didn't occur?

Third, it would not be clear what is meant by "applied location". If it is applied topically to the skin or the lining of the lung, does the "applied location" cover only the skin and lung lining, or would the tissue right below the skin or lung lining be considered part of the same location? In addition, if the answer to that is "yes", a drug on the skin is applied to the epidermis. Is it just the epidermis" which is considered the applied location, or is the dermis, and the hypodermis also considered part of the same location. In other words, if the drug applied to the epidermis showed an effect in the hypodermis, is that the applied location or beyond the applied location?

Claim 121 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

How far does "locally" extend? If it is applied topically to the skin or the lining of the lung, does the "locally" cover only the skin and lung lining, or would the tissue right below the skin or lung lining be considered part of the same location? In addition, if the answer to

that is "yes", a drug on the skin is applied to the epidermis. Is it just the epidermis which is considered local, or is the dermis, and the hypodermis also considered part of the same location.

In addition, the "and does not raise interferon levels when administered orally" is extremely unclear. First, note that "topical" does cover not only the surface of the skin and surface of the lungs (the most common types), but also the surface of the mouth, which is treated by oral medicines. A topical oral composition assists with dental wound healing, or can reduce tooth decay, alleviate oral pain (e.g. Benzocaine topical oral lozenge), or treat oral mucositis (e.g. with filgrastim as a mouthrinse). Topical oral sprays are frequently used to prevent and manage oropharyngeal inflammation and lesions. A chewing gum or a lozenge can be used as a topical oral medicine for halitosis caused by bacteria in an oral cavity. In short, while applicants apparently intended "topical" and "oral" as non-overlapping categories, they do in fact overlap, which would produce a contradiction.

Further, even if applicants intend "topical" not to cover "oral", this is still unclear. The claim calls for topical administration, so that the "when administered orally" isn't being done in the first place (unless applicants are talking about a simultaneous administration of oral and topical, which seems extremely unlikely). On the other hand, it ay be intended as a limitation on the scope of compounds, i.e. applicants are intending to exclude from the scope of the claim compounds which meet Formula 1, but which raise levels if they are administered orally.

Claim 121 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The new language "interferon" is indefinite. The term "interferon" is incomplete; there is no such thing per se, but there is rather a large family of somewhat related species. These fall into 3 major classes:

A. Type I IFNs consists of 13 different alpha-IFN isoforms (leukocyte interferon), a single beta-IFN (fibroblast interferon), an omega-IFN , an epsilon-IFN and a kappa-IFN. In addition, IFN-zeta (limitin) is found in mice, IFN-nu in cats, IFN-tau in ruminants and IFN-delta in pigs has been identified.

B. The type II IFNs consists just of IFN-gamma.

C. The Type III is IFN-lambda with 3 different isoforms, and was only recently discovered (2003).

These operate via multiple signalling mechanisms, and bind at different places. Type I binds at a cell surface receptor complex consisting of IFNAR1 and IFNAR2 chains, while Type II binds to a complex, which is made up of IFNGR1 and IFNGR2 subunits and Type III uses complex consisting of IL10R2 and IFNLR1. These also have different origins. Interferon-alpha is produced in leukocytes, Interferon-beta is produced in fibroblasts, or in epithelial cells, and Interferon-gamma is produced in certain activated T-cells and NK cells. The gene encoding IFN-kappa is expressed in epidermal keratinocytes. IFN-tau is produced in trophoblasts.

Much about these is unclear. For example, biological activities and the physiological role of omega-IFN are unknown, although it may have some anti-tumor activities.

For whichever choice is selected, applicants must show that one skilled in the art could have figured out that this choice, and not another, was surely intended.

Claim 123 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "9122" in line 1 is not correct.

Claim 104 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. No definition for Y2 appears.

B. The definitions for r1 and r2 as counting numbers appears, but these numbers are not in use.

C. The material at the end of the claim, formulas (3)-(6) is of unknown function. Note that the Q1 definition was already closed by the "or" before OCONR11R12.

Claims 89-99, 110-115, 117-119 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Such a scope of utility (beyond the 2 disorders of claim 116) cannot be deemed enabled.

Pursuant to ***In re Wands***, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), one considers the following factors to determine whether undue experimentation is required: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the

prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Some experimentation is not fatal; the issue is whether the amount of experimentation is "undue"; see ***In re Vaeck***, 20 USPQ2d 1438, 1444.

The analysis is as follows:

(1) Breadth of claims.

(a) Scope of the compounds. Because of the broad scope of Q1, Q2, A and Y2, trillions of compounds are covered.

(b) Scope of the diseases covered.

A. Regulating immune response (now only in claim 114) is embracive of treating autoimmune disorders. The "autoimmune diseases" are processes that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are dozens of such diseases, which have fundamentally different mechanisms and different underlying causes. Known autoimmune disorders, or disorders generally considered to be autoimmune include Polymyositis, Scleroderma, Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), Meniere's disease, Omenn syndrome, Idiopathic neutropenia, Idiopathic thrombocytopenic purpura, Autoimmune hemolytic anemia, Premature ovarian failure, Idiopathic hypoparathyroidism, primary biliary cirrhosis, Pemphigus, multiple sclerosis, autoimmune uveitis, rheumatoid arthritis, Addison's disease, Silent thyroiditis, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, hemolytic anemia,

systemic lupus erythematosus, Wegener's granulomatosis, polyarteritisnodosa, erythema nodosum leprosum, Guillain-Barré syndrome (GBS), allergic encephalomyelitis, acute necrotizing hemorrhagic encephalopathy, idiopathic bilateral progressive sensorineural hearing loss (IPBSNHL), aplastic anemia, pure red cell anemia, polychondritis, scleroderma, Stevens-Johnson syndrome, Alopecia areata, asthma, idiopathic sprue, lichen planus, Crohn's disease, Graves ophthalmopathy, sarcoidosis, primary biliary cirrhosis, type I diabetes, autoimmune optic neuritis, uveitis posterior, or interstitial lung fibrosis, Reiter's syndrome, Sjogren's Syndrome, Goodpasture Syndrome, inflammatory bowel disease, Essential Mixed Cryoglobulinemia, Behçet's Syndrome, Chronic Inflammatory Polyneuritis (CIPD), CREST Syndrome, Antiphospholipid Syndrome, Relapsing Polychondritis (systemic chondromalacia or von Meyenburg disease), Retroperitoneal Fibrosis, Celiac disease, Vitiligo, "immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome" (IPEX), Autoimmune Atherosclerosis and many more.

B. Claims 89-99, 110-114, 117-119 are drawn to allergic diseases, and 114 is embracive of this. The term "allergies", "allergic diseases" and the like are fairly broad, and are used is somewhat different ways by different people, and as a result, it is not always clear what the term denotes. There are four major categories that are normally included:

A. Atopic IgE mediated, e.g. eczema, allergic rhinitis and most forms of asthma

B. Non-atopic IgE mediated, including reactions to insect and spider bites, and reactions to certain drugs

C. IgG mediated, e.g. allergies to casein and other milk proteins, and gluten. (Type III Hypersensitivity)

D. T-cell mediated allergies, including poison ivy, nickel contact dermatitis, other forms of Allergic contact dermatitis. (Type IV Hypersensitivity, also called cell-mediated or delayed-type hypersensitivity, DTH).

Other types of reactions may or may not be considered as allergies. Thus, type II hypersensitivity is a cytotoxic reaction which involves IgM or IgG or both, including e.g. ABO incompatibility reaction, Rhesus disease may or may not be considered an allergy reaction. It is unclear whether aspirin sensitivity is an allergy or an intolerance. Whether there is such a thing as fluoride allergy is contested. Some consider all reaction to ordinary food additives as intolerance, but others believe that some of these are in fact allergic reactions.

C. "Regulating" (now only in claim 114) would also include the opposite effect, where the cellular and/or humoral immune system is stimulated to cope with immunoinsufficiency arising from irradiation, chemotherapy, HIV, genetic disorders, age-associated damage etc. There are a significant number of Immunodeficiency Disorders, in two very different categories. Primary Immunodeficiency disorders are caused by inherited functional defects in the cells of the immune system, particularly B and/or T Lymphocytes. Examples include X-linked Agammaglobulinemia (Bruton's disease), Common Variable Immunodeficiency , Selective IgA Deficiency, DiGeorge Syndrome , Severe Combined Immunodeficiency Disease (SCID, which is actually heterogeneous group of conditions all associated with genetic defects in those lymphoid stem cells that are precursors for both T and B Lymphocytes. This causes functional impairment of both humoral and cell-mediated immunity), Wiskott-Aldrich syndrome, Ataxia-Telangiectasia , and other inherited defects in the complement system, and defects in granulocyte function. Secondary immunodeficiencies are acquired

defects in immune function resulting from a wide variety of soruces. These include drugs (e.g. cancer chemotherapeutic agents, Cyclosporin, and corticosteroids), infections of immune system cells (most notably HIV), disseminated cancers (malignancies that invade the bone marrow may crowd out immune system cells and their precursors), malnutrition, radiation therapy (bone marrow suppression, lymphocyte toxicity), Splenectomy (increased susceptibility to infection by encapsulated microorganisms), severe burns (loss of immunoglobulins through damaged skin) and chronic renal disease.

(2) The nature of the invention and predictability in the art: The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See ***In re Fisher***, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(3) Direction or Guidance: That provided is very limited. The dosage range information provided for external administration appears only in the last full sentence on page 43. However, this does not give any amounts, any daily dosage, just a broad concentration range. Further, it is completely generic. That is, it is the same dosage for all disorders listed in the specification, which is a very substantial range of disorders.

(4) State of the Prior Art: The compounds are 8-hydroxy adenines with a particular substitution patters in the 2-position and 9-position. So far as the examiner is aware, no 8-hydroxy adenines of any kind at all are presently in use for the treatment of any immune-oriented disorder.

(5) Working Examples: There are no working examples to the treatment of any actual disorder. Examples 122 and 123 provide an in vitro test showing the stimulation of the

production of an unspecified type of interferon. Example 126 shows the nasal administration to an asthma-model mouse, showing the one compound tested to be somewhat less effective that Beclometasone dipropionate.

(6) Skill of those in the art: This very much depends on the particular art area. In fact, there are four basic mechanisms underlying autoimmune disease: 1. Antibody mediated diseases: a specific antibody exists targeted against a particular antigen (protein), which leads to its destruction and signs of the disease. Examples are: auto-immune mediated hemolytic anemia, where the target is on the surface of the red blood cell; myasthenia gravis where the target is the acetylcholine receptor in the neuromuscular junction; hypoadrenocorticism (Addison's) where the targets are the cells of the adrenal gland. 2. Immune-complex-mediated diseases: antibodies are produced against proteins in the body. These combine into large molecules that circulate around the body. In systemic lupus erythematosus (SLE) antibodies are formed against several components in the cell's nucleus (hence the anti-nuclear antibody test (ANA) for SLE). Most notably antibodies are made against the body's double stranded DNA, and form circulating soluble complexes of DNA and antibody, which break down in skin causing an increased sensitivity to ultraviolet light and a variety of signs. As the blood is filtered through the kidneys, the complexes are trapped in the glomeruli and blood vessels, causing the kidney to leak protein - glomerulonephritis. They also cause leakage in other blood vessels, and there may be hemorrhaging, as well as accumulating in synovial fluid and causing signs of arthritis and joint pain. Rheumatoid arthritis results from immune complexes (IgM class antibody called rheumatoid factor) against part of the patient's own immune system (part of its IgG molecules). These form complexes that are deposited in the synovia of the joint spaces

causing an inflammatory response, joint swelling, and pain. The collagen and cartilage of the joint breaks down and is eventually replaced by fibrin which fuses the joints - ankylosis. 3. Antibody and T Cell-mediated diseases: T cells are one of two types (the other being B-cells), which mediate immune reactions. Upon exposure to a particular antigen, they become programmed to search for and destroy that particular protein in future. Once a patient has been exposed to an antigen, he will be able to mount a much faster response to it the next time it encounters it. This is the basis of vaccination. Thyroiditis (autoimmune hypothyroidism) seems to be of mixed etiology. Several target antigens have been identified, including thyroglobulin the major hormone made by the thyroid. Auto-antibodies to antigens in the epithelial cells of the thyroid have also been found. The thyroid becomes invaded by large numbers of T and B cells as well as macrophages, which are cells that engulf and destroy other cell types. T cells specifically programmed for thyroglobulin have been identified. Autoimmune disorders can arise from the killer T-cells, from the helper T-cells, or from the regulatory T-cells (e.g. IPEX syndrome). 4. Diseases arising from a deficiency in complement: When an antigen and antibody react they may activate a series of serum enzymes (the complement system) whose end result is either the lysis (breakup) of the antigen molecule or to make it easier for phagocytic cells like the macrophages to destroy it. Patients with deficiencies in enzymes activated early in the complement system develop autoimmune diseases like SLE. Thus, with such differing mechanisms, it is not logical that a treatment for autoimmune diseases generally can be found.

Examples of pharmaceutically untreatable autoimmune disorders include celiac disease, APECED, and ALS. Medicines can be given to relieve symptoms, e.g. replace

missing hormones or ameliorate pain, but these pharmaceuticals do not treat the disease itself.

Basically, there are two immune system, cell and humoral, and the claims cover both increasing and decreasing both of them, i.e. four different effects. Further, there are many different regulators involved in allergic reactions, including two different types of T-cells, IgE, IgM, IgG, B cells and others. Such a scope cannot possibly be deemed enabled.

(7) The quantity of experimentation needed: Especially in view of points 1, 4, 5 and 6, the amount is expected to be high.

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. ***In re Wright***, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here.

The earlier traverse was unpersuasive. Applicants pointed to their evidence of anti-interferon activity. These claims, however, are not drawn to the induction of interferon activity; the term "interferon" does not even appear. Moreover, this is actually an argument against enablement for this scope. As noted previously, the specification fails to state which interferon this is. Assuming that it is IFN-gamma, that means that that applicants compounds increase the production of IFN-gamma. The claim language of "regulating immune response" would of course cover treatment of auto-immune diseases, since these are an extremely important area where the immune response needs to be regulated. However, IFN-gamma has been implicated in pathology of some of the most

important autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, insulin-dependent diabetes mellitus (Type 1) and autoimmune nephritis. Thus, again assuming that this is IFN-gamma, treatment of these diseases cannot be considered enabled because applicants agents would be expected to make these diseases worse.

Applicants next pointed to the success with asthma and applicants do so again in the response of 02/23/2009. The asthma claim is not rejected, nor was the previous asthma claim, claim 78.

Applicants next stated, "The Examiner commits reversible error by requiring certainty with respect to pharmaceutical efficacy as a criterion for patentability." The examiner has not said or implied any such standard.

Next, Applicants stated, "Rather, Applicants' burden is only one of the preponderance of the evidence, meaning that the specification and any post-filing data submitted must only establish that it is more likely than not that the invention will work as asserted." Applicants have not presented any citation for this assertion. Indeed, ***In re Ferens***, 163 USPQ 609 says "Evidence submitted to establish usefulness must be such as would be clear and convincing to one of ordinary skill in the particular art." (emphasis added), which is a higher standard. In this regard, applicants cite MPEP 706(I) which states, "The standard to be applied in all cases is the "preponderance of the evidence" test. In other words, an examiner should reject a claim if, in view of the prior art and evidence of record, it is more likely than not that the claim is unpatentable." This is a somewhat different circumstance. The MPEP is talking about the general circumstance where there is evidence on both sides of the question of patentability. Ferens is talking about a specific circumstance where the burden is on applicants to establish usefulness.

Applicants argued that the standard is "undue experimentation", but that is the standard which the examiner did quote.

Applicants stated, "The present specification discloses a large number of compounds and demonstrates efficacy for the intended utility in vitro and in vivo." This is simply not true, because the scope of "the intended utility" is vastly broader that the testing shown. Applicants have shown asthma, and some unspecified IFN. The scope of "regulating immune response" is far broader than that, as 1) many immune disorders such as the autoimmune disorders, AIDS, food allergies, are totally unrelated to asthma and 2) there are many immune disorders, and types of immune responses, which have absolutely no (known) connection to IFN-gamma. They are instead mediated by IgG, IgE, B-cells, antibodies, several different types of T-cells, the three different complement system pathways (none of which use IFN-gamma) and more.

Applicants in the response of 02/23/2009 state: "The Examiner states that "physiology is generally considered to be an unpredictable factor." (Office Action, page 14). Applicants disagree. The Examiner does not support this statement with any documentary evidence, and the statement is so broad as to be meaningless to the present application. For instance, physiology could be anything from aging to cancer. Aging is predictable. Some cancers may not be." Aging in the sense of getting one day older each day is predictable. Aging in the sense of physiology is not, since hundreds of different processes are involved in physiological aging, and these proceed in often unpredictable forms. The immune system is actually one of the less predicable parts of the body, in part because it is so often a mystery why one person's immune system overreacts and another does not, or why one part of the body's overall immune system reacts and another does not.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., ***In re Berg***, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); ***In re Goodman***, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); ***In re Longi***, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); ***In re Van Ornum***, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); ***In re Vogel***, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and ***In re Thorington***, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 89-95, 97-103, 105-108, 110-120, are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-19, 21 of copending Application No. 10594074. Although the conflicting claims are not identical, they are not patentably distinct from each other because there is substantial overlap when in 10528343, m=1. For example, the species 9-(3-carboxymethylbenzyl)-2-(2-ethoxyethoxy)-8-hydroxyadenine of 10594074 falls within the claims of 10528343 for m=1, Y2=methylene, and Q1=alkoxy.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The traverse is unpersuasive. Applicants note that the claims have not been issued, which is true. That is why the rejection is labeled as provisional.

7157465 is noted, which has claims embracive of these, but no species appears which anticipates or renders obvious the claims here.

In the event applications corresponding to WO 2007034917, WO 2007034817 or JP 2005089334 are filed with the PTO, applicants are to inform the examiner of this.

Claim Objections

Claim 132 is clearly garbled; the "120. (currently amended)" needs to be removed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to /Mark L. Berch/ whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Mark L. Berch/

Primary Examiner
Art Unit 1624

5/1/2009